UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: 8 Month RED Response: Zinc RED
EPA Reg. No./File Symbol: 802-591 & 10699-1
802-508 & 802-553

From: JoAnne Hayes, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)
JH 2-9-94

To: Joanne I. Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)
E 3/3/94

Applicant: The Chas. H. LILLY Co. and Retta Mfg, Inc
7737 NE Killingsworth P.O. Box 2306
Portland, OR 97218 Eugene, OR 97402-0073

FORMULATION FROM LABEL: (subject products 802-591 & 10699-1)

Active Ingredient(s)::	% by wt.
Zinc Sulfate Monohydrate	99%
Inert Ingredient(s):	1%
Total:	100%

BACKGROUND: The registrants, the Chas. H. LILLY Co. and Retta Manufacturing, jointly submitted an acute dermal toxicity study, acute inhalation toxicity study, and a dermal sensitization study to support reregistration of the subject products. The toxicity for acute oral toxicity, primary eye irritation, and dermal irritation are provided by the Zinc RED. The PRAT sheet for this submission stated that the studies were submitted to support EPA Reg No.s 802-508, 802-553, 802-591, and 10699-1.

RECOMMENDATIONS: The studies submitted were performed on EPA Reg No. 802-591, and support reregistration of the products 802-591 and 10699-1. The products 802-591 and 10699-1 are included in Batch 2 of the RED. Therefore, studies performed on 802-591 can also support reregistration of 10699-1.

The products 802-508 and 802-553 are not supported by these studies. Registrations 802-508 and 802-553 are formulations of zinc chloride at 29.6% and 6.2% respectively, and are not included in any RED batches. These formulations are not considered similar to the test material, and cannot be supported by the submitted studies.

The acute dermal toxicity and acute inhalation toxicity studies are acceptable, and graded core minimum. The studies can be upgraded to core guideline if more information on the phase of the study inspected during the Quality Assurance Inspection is provided. Future studies should include a detailed report on the Quality Assurance Inspection.

The dermal sensitization study is not acceptable and graded core supplementary. The registrants must submit another dermal sensitization study to support reregistration of the products 802-591 and 10699-1. The dose concentration used at induction may not have been sufficient to induce sensitivity in the test animals. According to Ritz (1980), the induction dose irritation is not of concern unless frank necrosis results from its application. Additionally, Robinson (1990) indicates that the induction concentration used should elicit mild to moderate irritation which would be identified as scores of 1 and 2 on the Buehler scale. The study elicited a majority of scores at ± during the range finding study, and only ± during all three induction phases, indicating an insufficient concentration of the test material at induction. To insure induction of sensitization, the highest non caustic concentration of test material should be utilized. The lab should review the following for further information on the choosing of the induction dose:

Ritz, H.L. and Buehler, E.V. 1980. Planning, Conduct and Interpretation of Guinea Pig Sensitization Patch Tests. *Current Concepts in Cutaneous Toxicity*, (V.A. Drill & P.Lazar, ED) p 25-40. New York, Academic Press.

Robinson, M.K., et. al. 1990. A review of the Buehler guinea pig skin sensitization test and its use in a risk assessment process for human skin sensitization. *Toxicology*, 61. p 91-107. Ireland, Elsevier Scientific Publishers Ireland Ltd.

The toxicity profile for the products 802-591 and 10699-1:

Acute Oral	III/RED derived
Acute Dermal	III/Minimum
Acute Inhalation	III/Minimum
Eye Irritation	I/RED derived
Dermal Irritation	IV/RED derived
Dermal Sensitization	—/Supplementary

LABELING:
1. The Hazard Signal Word is "DANGER".

2. The Precautionary Statements should read as follows:

Corrosive. Causes irreversible eye damage. Harmful if swallowed, inhaled or absorbed through skin. Do not get in eyes or on clothing. Wear goggles or safety glasses. Avoid contact with skin and breathing dust. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

3. The Statement of Practical Treatment should read as follows:

IF SWALLOWED: Drink promptly a large quantity of milk, egg white, gelatin solution or, if these are not available, large quantities of water. Avoid alcohol. Get medical attention.
IF IN EYES: Hold eyelids open and flush with a steady gentle stream of water for 15 minutes. Get medical attention.
IF ON SKIN: Wash with plenty of soap and water. Get medical attention.
IF INHALED: Remove victim to fresh air. If not breathing, give artificial respiration, preferably, mouth-to-mouth. Get medical attention.
NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

4. Further labeling statements may be required after submission of the required dermal sensitization study.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: J. Miller
Reviewer: J. Hayes
MRID No.: 426950-01
Report Date: 2-9-93
Author(s): Geoffrey Robbins
Report No.: B3323
Testing Laboratory: Cosmopolitan Safety Evaluation, Lafayette, NJ
Test Mater.: EPA Reg. No. 802-591
Supporting:802-591 & 10699-1
Species: New Zealand White Rabbit
Age: young adult
Sex: M (5) F(5)
Weight: M = 2.50 - 3.10 kg F = 2.50 - 2.90 kg
Quality Assurance (40 CFR §160.12): yes _X_ no ___

Summary:

1. LD_{50}	**(mg/kg)**	**95% Conf. Limits**	
Males =	—	———	
Females =	—	———	
Combined =	—	———	

2. **The estimated LD_{50} is** > 2 g/kg
3. **Tox. Category**: III **Classification**: Core minimum

Procedure (Deviation From §81-2): —
Quality Assurance Inspection report included insufficient information on phase of study inspected.

Results: Reported Mortality

DOSAGE	(NUMBER KILLED/ NUMBER TESTED)		
	Males	Females	Combined
2 g/kg	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:
Clinical symptoms were moderate irritation at 45 min after removal of wrap with erythema of grade 1 or 2 and grade 1, 2 or 3 edema. On Day 3 grade 1 or 2 erythema and grade 1 or 2 edema was observed. Day 7 all sites were edema free with 6/10 sites still showing grade 1 erythema. All sites normal on Day 14. No corrosive effects or in depth injury noted.
Necropsy showed no abnormal signs.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: J. Miller
Reviewer: J. Hayes
MRID No.: 426950-02
Report Date: 2-26-93
Author(s): Geoffrey Robbins
Report No.: C3323
Testing Laboratory: Cosmopolitan Safety Evaluation, Lafayette, NJ
Test Mater.: EPA Reg. No. 802-591
Supporting:802-591 & 10699-1
Species: Sprague Dawley Rat
Age: Young adult
Sex: M (5) F (5)
Weight: M = 262 - 283 g F = 205 - 229 g
Quality Assurance (40 CFR §160.12): yes X no ___

Summary:

1. LD_{50}	(mg/kg)	95% Conf. Limits
Males =	—	———
Females =	—	———
Combined =	—	———

2. **The estimated LC_{50} is** > 1.46 mg/l
3. **Mean Concentration**: 1.46mg/l
4. **Tox. Category**: III **Classification**: Core Minimum

Procedure (Deviation From §81-3):—
Quality Assurance Inspection report included insufficient information on phase of study inspected.

Results: **Reported Mortality**

Exposure Concentration	(NUMBER KILLED/ NUMBER TESTED)		
	Males	Females	Combined
1.46 mg/l MMAD 1.5um, GSD N.D.	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:
Clinical symptoms were transient yellow perineal staining in one male animal, and perineal staining and occasional chromodacryorrhea with recovery by the following day. Some reduced weight gain during the first 3 days following the study, but normal weight gain resumed thereafter.
Necropsy revealed no abnormalities.

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: J. Miller **Reviewer:** J. Hayes
MRID No.: 426950-03 **Report Date:** 2-26-93
Author(s): Geoffrey Robbins **Report No.:** F3323
Testing Laboratory: Cosmopolitan Safety Evaluation, Lafayette, NJ
Test Mater.: EPA Reg. No. 802-591 **Supporting:**802-591 & 10699-1
Species: Guinea Pigs
Weight: 415 - 491 g
Source: Camm Research Lab Animals , Wayne, NJ
Positive Control Material:p-phenylenediamine
Quality Assurance (40 CFR §160.12): yes _X_ no ___

Method: Buehler

Summary:

1. **Dermal sensitization could not be determined from this study.**

2. **Classification:** Core Supplementary

Procedure (Deviation From §81-6):
Only male animals used to avoid inconsistencies due to the estrus cycle.
Induction dose may be too dilute to induce sensitization.
(Challenge dose correctly chosen at 25%.)

Results:
A range finding study was performed with 50%, 25%, 10%, and 5% w/w test material. The 50% dose elicited 24 hour observation scores of 4/5 at ± and 1/5 at 1. The 25% dose elicited 5/5 scores of ±. The grade ± is considered negative in the Buehler scoring system.
Induction was performed at 50% conc. and elicited 24 hour scores of 6/10 at ± and 4/10 at 0. Scores at 24 hours through the second and third inductions were 8/10 at ± 2/10 at 0, and 7/10 at ± and 3/10 at 0 respectively.
A 25% conc. of test material was used for challenge. The 24 hr observation elicited 4/10 at ± and 6/10 at 0. Naive controls treated with the 25% conc. elicited 2/5 at ± and 3/5 at 0.

ACUTE TOX ONE-LINER

1. PC CODE: 527200

2. CURRENT DATE: 3/3/94

3. TEST MATERIAL: Zinc Sulfate Monohydrate 99%

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
Acute dermal/NZWRabbit/Cosmopolitan Safety Evaluation/B3323/2-9-93	426950-01	no mortality @ 2g/kg	III	Min
Acute Inhalation/SDRat/ Cosmopolitan Safety Evaluation/C3323/2-6-93	426950-02	no mortality @ 1.46mg/l	III	Min
Dermal Sens/Guinea Pig/ Cosmopolitan Safety Evaluation/F3323/2-26-93	426950-03	not acceptable	---	Suppl.

Core Grade Key:

G = Guideline
M = Minimum
S = Supplementary